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Toxicogenomics

EHP Toxicogenomics: Research Article

Phenotypic anchoring of gene expression changes during estrogen-induced uterine growth.

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Abbreviations:

ER – estrogen receptor

ANOVA – analysis of variance

AO – arachis oil

E_2 – 17β-estradiol

sc – subcutaneous

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Abstract

A major challenge in the emerging field of toxicogenomics is to define the relationships between chemically induced changes in gene expression and alterations in conventional toxicological parameters, such as clinical chemistry and histopathology. We have explored these relationships in detail using the rodent uterotrophic assay as a model system. Gene expression levels, uterine weights and histological parameters were analyzed 1, 2, 4, 8, 24, 48, and 72 hr after exposure to the reference physiological estrogen, 17β-estradiol (E_2). A multi-step analysis method, involving unsupervised hierarchical clustering followed by supervised gene ontology driven clustering, was used to define the transcriptional program associated with E_2-induced uterine growth and to identify groups of genes that may drive specific histologic changes in the uterus. This revealed that uterine growth and maturation is preceded and accompanied by a complex, multi-stage molecular program. The program begins with the induction of genes involved in transcriptional regulation and signal transduction, and is followed, sequentially, by the regulation of genes involved in protein biosynthesis, cell proliferation and epithelial cell differentiation. Furthermore, we have identified genes with common molecular functions that may drive fluid uptake, coordinated cell division and remodeling of luminal epithelial cells. These data define the mechanism by which an estrogen induces organ growth and tissue maturation, and demonstrate that comparison of temporal changes in gene expression and conventional toxicology endpoints can facilitate the phenotypic anchoring of toxicogenomic data.